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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,535	02/20/2001	Guy Rousseau	VANM198.001A	7462

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EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/763,535	Applicant(s) ROUSSEAU ET AL.	
	Examiner Sita S Pappu	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary amendment filed on February 20, 2001 has been entered. Claims 1-8 are amended and claim 9 has been added.

Claims 1-9 are pending in the instant application. This paper contains an examination of the claims 1-9 on their merits.

Drawings

Drawings are objected to by the draftsperson. See attached PTO-948. Drawings are acceptable for examination purposes only.

Specification

The abstract is not on a separate sheet of paper as required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-6 are directed to a pharmaceutical composition comprising a polynucleotide encoding a peptide of the ONECUT gene family, wherein the polynucleotide can be an isoform of HNF-6 or OC-2 or OC-3 from humans, a vector

comprising the said polynucleotide , the polypeptide encoded by the said polynucleotide, and a cell line transformed with said vector.

While the specification is enabling for a polynucleotide encoding HNF-6 or OC-2 or OC-3, no pharmaceutical property is shown and/or enabled by the specification for the reasons discussed herein below. Thus the specification does not enable one skilled in the art to make and use the claimed invention.

Claims 7-9 are drawn to a method of using the polynucleotide of claim1 in gene therapy for the prevention and/or for the treatment of diabetes, cancer, and Waardenburg syndrome. The specification does not disclose the use of these polynucleotides in gene therapy. Nor does it disclose the use of these polynucleotides in the treatment of any disease(s). Thus the specification is not enabling for the use of these agents in gene therapy and/or for the treatment of any of the diseases. The specification states that HNF-6 is essential in $HNF6^{-}$ knockout mice, for the functioning and formation of the islets of langerhans and for the response of the organism to insulin (see page 4, lines 9-13). Further, the specification only discloses that the diabetes of the $HNF6^{-}$ knockout mice is spontaneously cured with an increase in OC2 in pancreas (page 4, lines 31-34). Other than this, the specification does not disclose any pharmaceutical property for the said polynucleotide in the form of a composition. Prophetic examples of how diabetes can be induced in rats followed by how cells that are stably transfected with the said polynucleotide in a vector can be injected into the said diabetic rat are provided (page 13, lines lines 17-19, 21-24; page 14, lines 11-17). These examples in the specification do not disclose the phenotype or behavior of the

said rat after injecting the said cells into the rat and/or the efficacy of the polynucleotide in treating the diabetes in the rat. In the absence of specific guidance, one of skill in the art would be required to engage in undue experimentation to make and use the invention as claimed.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

In the instant case, the claims 1-9 are drawn to a pharmaceutical composition and a method of using the said composition in the prevention and/or treatment of diabetes, cancer and/or Waardenburg syndrome. The specification teaches only polynucleotides of the ONECUT family but fails to disclose any pharmaceutical property or the mode of using the said polynuelotide in treating the claimed diseases. The specification does not teach how to make and use the invention as claimed. Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as

specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (Sigmund, 2000, pg.1425, paragraph 1). Further, the particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, in the absence of specific guidance and working examples, the use of the claimed polynucleotide composition in the treatment and prevention of diseases is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples directed to rats, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention over any scope as claimed.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2). Marshall

concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Further, Halban et al. (2001; Diabetes, volume 50, pp2181-2191) in their review on the gene and cell-replacement therapy in the treatment of diabetes caution that "we not forget the age-old adage that a rodent is not a human in more ways than just appearance" (page 2187, left column, paragraph 2, lines 5-7). Halban et al. further state that the use of rodent models may be useful for certain aspects of the metabolism, it has the potential to be misleading for others, including glucose disposal (page 2187, left column, paragraph 3, lines 1-4). They further state that when using animal models to test new systems, one must keep in mind that the efficacy of glucose uptake by insulin-independent mechanisms in animals is commonly greater than in humans and that simply translating animal findings as the likely observation in humans may be risky (page 2187, left column, paragraph 3, lines 26-31).

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acid vectors, and the unpredictability of extending the results of animal systems to humans, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells, the lack of guidance concerning the treatment of diabetes, cancer, and Waardenburg syndrome using the polynucleotide of the instant invention, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in treating or preventing the wide variety of diseases as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemaigre et al. (1996; PNAS vol. 93, pp 9460-9464).

Although the composition is not enabled for its intended use as a pharmaceutical, the composition itself is disclosed in the prior art. The polynucleotide that comprises the pharmaceutical composition of claims 1 and 2, was anticipated by Lemaigre et al. (1996). Lemaigre et al. disclose the nucleotide sequence of HNF-6, a member of the ONECUT family. They disclosethat this sequence has been deposited in the GenBank data base under the accession number X96553. See page 9460, right column, Foot Note; page 9460, abstract; and page 9462, Figure 2).

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Lannoy et al. (1998; Journal of Biological Chemistry, vol. 273, no.22, pp 13552-13562).

Although the composition is not enabled for its intended use as a pharmaceutical, the composition itself is disclosed in the prior art. Lannoy et al. (1998) disclose the sequences of the two isoforms of HNF-6 which sequences were submitted to GenBank under the accession number Y14933. See page 13552, Foot Note and page 13554, left column, first paragraph in the results section.

Claims 3, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacquemin et al. (1999; Journal of Biological Chemistry, vol. 274, no.5, pp 2665-2671).

Although the composition is not enabled for its intended use as a pharmaceutical, the composition itself is disclosed in the prior art. Jacquemin et al. (1999) disclose the nucleotide sequence of human OC-2, a member of the ONECUT family (see page 2666, Fig. 1A). Jacquemin et al. (1999) disclose the OC-3 sequence in Fig. 1B on page 2667. The OC-3 sequence is disclosed indirectly in Jacquemin et al. Fig. 1B discloses two sequences: sequence of fosmid F37502 and cosmid F21967. On page 2670, paragraph 2, they disclose that these sequences represent the OC-3 sequence.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Krolewski (1998; PCT International publication Number WO 98/23780).

Although the composition is not enabled for its intended use as a pharmaceutical, the composition itself is disclosed in the prior art. Krolewski discloses the use of plasmid and viral vectors carrying a polynucleotide of the ONECUT family, along with the use of cationic liposomes (page 17, lines 2-13), and thus, claim 6 is anticipated by Krolewski.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (9:00 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Crouch, acting SPE, can be reached on (703) 308-1126. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746 7442 for regular communications and (703) 746 7442 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group patent analyst, whose telephone number is (703) 305-2758.

S. Pappu
December 27, 2001

Deborah Crouch
DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~/630